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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/200,791	11/30/1998	THOMAS M. BEHR	018734/0161	9799

7590 01/28/2002

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EXAMINER
HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 01/28/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/200,791	BEHR ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21 and 23-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21 and 23-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *19* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

1. The request filed on 2/21/01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/200,791 is acceptable and a CPA has been established. An action on the CPA follows.

2. Claims 1-21 and 23-37 are pending.

Claims 1, 2, 18-19 have been amended.

Claims 1-21 and 23-37 are under examination.

Priority

3. The instant application is a CIP of 08/407899 filed 3/21/95. Claims 1 and 18 in the instant application recite the limitation of a method of reducing kidney retention of a protein conjugate that is not an antibody or an antibody fragment conjugate. This limitation is not seen in the 08/407899 application. As such claims 1-21, 23-37 are granted the priority date of the instant application, 11/30/98.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-4, 6, 8, 13-14, 18-19, 23-24, 26, 28, 33-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Hammond et al (Br. J. Cancer 67:1437-1439, 1993 (IDS #4) as evidenced by U. S. Patent 5,225,180 (issued 7/93)

The claims recite a method of reducing kidney retention of a protein conjugate comprising administering D-lysine and a protein conjugate to a patient and the protein conjugate is not greater than 60 kD, wherein the conjugate is a imaging isotope, wherein the solution is administered to the patient as a continuous infusion, wherein the conjugate is a radiolabeled hapten conjugate.

Hammond et al teach a method of administering to a patient a radiolabeled imaging protein conjugate with D-lysine to reduce the renal uptake in the kidney (see abstract and entire document). The solution was administered by continuous infusion (see page 1437). The protein conjugate of Hammond is not an antibody or antibody conjugate and is less than 60 kD. The protein conjugate of Hammond et al is a somatostatin analog which as evidenced by U. S. Patent 5,225,180, somatostatin is a tetradecapeptide (see column 1).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-21 and 23-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Behr et al (Cancer Research 55:3825-3834, 1995), and further in view of Grey et al (U. S. Patent 5,380,513, issued 1/10/95, IDS #4) and Raines et al (U.S. Patent 5,840,296, filed 10/15/97).

Claims 1-4, 6, 8, 13-14, 18-19, 23-24, 26, 28, 33-34 have been described supra. Claims 5, 7, 9-12, 15-17, 25, 27, 29-32, and 35-37 recite wherein the conjugate is a therapeutic isotope, a protein conjugate comprising a cytotoxic agent, administering

poly-D or poly-L-lysine wherein they have a molecular weight of 15-30 kD, wherein the compounds are administered by a bolus and orally administered,

Behr et al teach a method of reduction of renal uptake of a protein conjugate comprising a imaging or therapeutic moiety in a patient with addition of lysine and poly-lysine (15-30 kD) and the solutions were administered by iv or ip (see entire document). Behr et al does not teach a protein conjugate that is not an antibody conjugate or a conjugate comprising a ribonuclease. These deficiencies are made up for in the teachings of Grey et al and Raines et al.

Grey et al teach a method to reduce renal retention of protein conjugates with lysine (see abstract and column 3, lines 44 to column 4, lines 2). Grey et al teach the conjugates comprise imaging agents and therapeutic agents (see column 7), that comprise cytotoxins and the proteins comprise receptors and enzymes as well as other proteins (see columns 5-6) Grey et al also teach administration orally, iv, ip, or the like (column 6, lines 1-5).

Raines et al teach conjugates comprising ribonuclease which have been effective in tumor patients (see column 1) and the decrease in renal function of Onconase may be the consequence of an inability to effectively clear the Onconase protein from the kidneys (see column 2, lines 52-57). Onconase is a 104 amino acid protein (see column 2, lines 34-35) which is not greater than 60 kD.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method for reducing kidney

retention of protein conjugates in a patient with administration of compounds of lysine or poly-lysine in view of Behr et al, Grey et al, and Raines et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method for reducing kidney retention of protein conjugates in a patient with administration of compounds of lysine or poly-lysine in view of Behr et al, Grey et al, and Raines et al because Behr et al teach that kidney retention was reduced in conjugates by addition of lysine and poly-lysine and that poly-lysine (15-30 kD) was more effective in reducing renal uptake (see page 3829). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method for reducing kidney retention of protein conjugates in a patient with administration of compounds of lysine or poly-lysine in view of Behr et al, Grey et al, and Raines et al because Grey et al teach that protein conjugates comprising enzymes and added lysine can reduce renal uptake of the conjugates. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method for reducing kidney retention of protein conjugates in a patient with administration of compounds of lysine or poly-lysine in view of Behr et al, Grey et al, and Raines et al because Raines et al teach "A cytotoxic ribonuclease that is readily cleared from the kidneys would be less likely to cause renal toxicity" (see column 2, lines 58-62). Thus it would have been obvious to one of ordinary skill in the art to produce a method of reducing renal uptake of protein conjugates that are not antibody conjugates in view of the teachings of Behr et al, Grey et al, and Raines et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

10. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
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